REMARKS

Claims 1 and 2 have been cancelled.

Claim 3 has been amended by deleting the phrase "to the treatment area" and replacing it with "across a wound on the surface of the skin." Support for the amendment can be found in the Specification on page 1, lines 10-11 and Example 1. In addition, a Markush group containing the hyaluronic acid derivatives previously named in claim 2 has been introduced.

Claims 6, 8, and 9 have been amended to correct grammar.

Claim 12 has been amended by deleting the phrase "guide channel" and correcting a misspelling of "combination."

Support for new claim 15 can be found in claim 6.

Support for new claims 16 and 17 can be found in the Specification on page 8, line 21 and lines 26-29. Support can also be found in Example 1, pages 27 and 28.

No new matter has been added.

Rejections Under 35 USC § 102

WO 99/04828 ('828)

The Examiner has rejected claims 1-12 as being anticipated by WO 99/04828 ('828). The Examiner contends that the '828 patent publication discloses hyaluronic acid derivatives that are (1) esterified with alcohols, (2) auto-cross linked esters, (3) cross-linked hyaluronic acid compounds, (4) hemiesters of succinic acid, (5) N-sulphated derivatives of hyaluronic acid and (6) amid derivatives. The Examiner also contends that these listed hyaluronic acid derivatives can be formulated as gels and pharmacologically active substances can be added. Lastly, the Examiner contends that these hyaluronic acid-based compositions are used to treat formation of post-surgical adhesion and scar formation. Applicants respectfully traverse.

Applicants have cancelled the claims to the composition. Thus, the rejection of claims 1 and 2 is moot.

Applicants have amended claim 3 to more clearly indicate that the method involves applying across a wound on the surface of the skin a pharmaceutical

composition of at least one of the listed hyaluronic acid derivatives. This element (**a wound on the surface of the skin**) is absent from the '828 patent publication. Indeed, the '828 publication is concerned with using hyaluronic acid derivatives to provide a physical barrier to stop bleeding of an anastomotic site and to prevent adhesions from developing between the vein, bowel, etc. and the surrounding tissues. This is a very different use from that disclosed in the instant application.

First, '828 is concerned with anastomotic surgery, which is the joining of two tube-like elements. Here, the tissue must be joined together to recreate the tube (e.g. vein, bowel, etc.) and, in the case of veins, to ensure that once blood flow is re-established, blood does not leak from the joined vessel. While page 51 of the '828 reference specifies that reduced scar formation around the treated vessels was obtained, lines 7-11 of the same page specify that the scarring process is relative to the vessel walls.

Vessel walls are made up of muscle fibers and elastic fibers, the percentage of which depends on the nature of the vessel itself (venous or arterial) and its diameter. Thus, the composition of vessels is distinct from that of the dermis/skin which is mainly constituted by connective tissue and which is absolutely without any muscle tissue (for a summary of the differences between muscle cells and connective tissue cells see pages 24 and 25 of Molecular Biology of The Cell, 2nd Edition, Albers, Bray, Lewis, Raff, Roberts and Watson, eds., Garland Publishing, Inc., New York, provided herewith). Because of the different cell types involved, any scarring that occurs on vessels results from a very different process than scarring of the dermis since very different cell types are involved.

Second, it is also critical in anastomotic surgery that adhesions do not form between the repaired tube and the adjacent tissue as this would cause other types of damage to the repaired site and surrounding organs. The biomaterials of '828 accomplish this task in two ways by providing (1) absorbent properties for body fluids and a physical haemostatic activity (see '828 abstract) and (2) by creating a physical barrier.

With respect to creating a physical barrier, De Iaco et al. (2001, *Surgery* 130:60-64, provided herewith) describe the use of biodegradable products that are applied to injured surfaces to cover and isolate the injured tissues until healing is complete (see page 63, column 1, last full paragraph) or by instilling polymeric absorbable solutions that

permit the organs to "float" and avoid prolonged contact between raw surfaces. Consequently, the ability of the '828 biomaterials to prevent adhesion formation is entirely based on a simple mechanical/physical effect of the biomaterials when used during anastomotic surgery.

In contrast, the instant invention is not concerned with re-establishment of a tube or prevention of adhesion formation with adjacent tissue/organs. Instead, the biomaterials are used to cover the site of a wound on the surface of the skin while tissue is generated that will ultimately fill in the wound and re-establish an unbroken area of skin that is similar in texture, appearance and flexibility to the unwounded surrounding area. Therefore, not only does the '828 reference lack any disclosure regarding scarring of skin tissues, but the understanding at the time was that adhesion prevention resulted from isolation of the wound. Thus, Applicants respectfully request reconsideration and removal of the rejection.

WO 97/07833 ('833)

The Examiner has rejected claims 1-8 and 12-13 as being anticipated by WO 97/07833 ('833). The Examiner contends that the '833 publication discloses the following set of hyaluronic acid derivatives: (1) hyaluronic acid esterified with alcohols, (2) auto-crosslinked esters and (3) crosslinked hyaluronic acid compounds. The Examiner notes that the hyaluronic acid derivatives can be formulated as gels and additional pharmacologically active substances can be added. He also contends that '833 teaches hyaluronic acid derivatives used for post-surgical adhesion and states that '833 defines "adhesion" as a permanent scar that connects to adjacent surfaces. Applicants respectfully traverse.

Applicants first note that claims 1 and 2 have been cancelled thereby making these rejections moot.

Claim 3 has been amended by introducing an element which requires applying the hyaluronic acid derivative composition or biomaterial across **a wound on the surface of the skin**. This element is not taught in '833, which is directed towards preventing the adhesions that form between adjacent tissues after surgery. While the Examiner's

statement that '833 defines an adhesion as a permanent scar that connects two adjacent surfaces is partly true, the Examiner has taken this statement out of context. A skilled artisan reading the entire paragraph beginning at line 1 of page 2 would see that an adhesion appears to be formed as a result of an inflammatory response due to the release of serosanguinous exudates which form a fibrinous bridge between adjacent tissues.

While it was later suggested that the efficacy of hyaluronic acid derivative gel in the prevention of postsurgical adhesions is related to its barrier function rather than to any anti-inflammatory activity (Belluco et al. (2001) *Journal of Surgical Research* 100:217-221, page 220, column 1, first paragraph, provided herewith and De Iaco et al. discussed above), the adhesions that do form after surgery are **significantly different** from the scar that appears on the skin after a surface wound.

A wound on the surface of the skin that forms a scar is not the result of adhesions between two different and adjacent tissues or organs that should not adhere. Instead it results from adhesion of **two skin tissues**. The skin healing process is very complex and has at least three different phases in which various components interact (*see* Cecil Textbook of Medicine, 1988, Wyngaarden and Smith, eds., Harcourt Brace Jovanovich, Inc., Philadelphia, page 2306, provided herewith). Here, application of the biomaterials does not prevent adhesions, but promotes adhesion of the skin in such a way that the adverse effects of scarring are diminished. Furthermore, unlike the simple, mechanical/physical role that the biomaterials play in '833, the hyaluronic acid derivatives used in the claimed method appear to play an active role and interact with various factors to favor correct adhesion between two adjacent epidermal tissues.

Furthermore, '833 teaches that the use of the hyaluronic acid biomaterials prevent any adhesions from forming, whether they be the result of a "normal" fusion or a "scarring" fusion. This is very different from the instant invention that **promotes adhesion and allows a wound on the surface of the skin to heal** and produce a surface that is uniform in appearance, flexibility and texture with the surrounding tissue.

In view of the above, Applicants respectfully request reconsideration and removal of the rejection.

Summary

As discussed above, neither the '**828** nor the **'833 references** teach a method for treatment of scarring on the skin comprising applying across a wound on the surface of the skin hyaluronic acid biomaterials and so **cannot support a novelty rejection**.

In view of the above, Applicants submit that all of the pending claims define novel, unobvious and patentable subject matter and respectfully request reconsideration of the rejections and allowance of the claims.

Should there be any outstanding matters that need to be resolved in the present application; the Examiner is respectfully requested to contact Susan W. Gorman (Reg. No. 47,604) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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Encls.: PTO/SB/08 and References (total of 5)